PATENT COOPERATION TREATY

REC'D 16 AUG 2005
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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

A7

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/000548	07.01.2005	16.01.2004

International Patent Classification (IPC) or both national classification and IPC
G01N33/68

Applicant
CIPHERGEN BIOSYSTEMS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

CORRECTED VERSION

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/000548

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/000548

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 65-67

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 65-67

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12-64
	No:	Claims	1-11
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-64
Industrial applicability (IA)	Yes:	Claims	1-64
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No search and consequently no examination have been carried out with respect to claims 65-67.

2. Claims 1-27, 31-58 and 60-64 are related to modified troponins, troponin interactors and anti-troponin antibody interactors which are no further characterized by claims 1-27, 31-58 and 60-64 themselves. Such molecules are characterized by the description and by claims 65-67 only in terms of generic modifications such as splice variants, post-translational modifications and enzymatic degradation products, and in terms of their mass-to-charge ratio. Such characterization does not allow to identify any essential technical features of the claimed entities, in particular amino acidic sequence and additional structural/chemical information of the claimed polypeptides or compounds. For this reason, the search has been limited to methods comprising capturing troponins and detecting modified troponins by mass spectrometry.

Re Item V

Reasoned statement with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statements

1. Reference is made to the following document:

   D1: Simpson et al., Clinical Chemistry, vol.48, no.6, supplement, 2002, A95.

2. The subject-matter of claims 1-11, with the limitation discussed in point III.2, is not novel (article 33(2) PCT).

a. D1 discloses a method for investigating disease-induced troponin modifications, in particular troponin modifications that occur in acute coronary syndrome (ACS), comprising:
   (i) homogenising and centrifuging heart left-ventricular tissue;
   (ii) subjecting the supernatant from (i) to affinity chromatography with anti-troponin I monoclonal antibody;

(iii) eluting the proteins bound to the affinity column with non-denaturing buffer;
(iv) subjecting eluates from (iii) to Western blot with antibodies against troponin I, troponin T and troponin C, and to MALDI-TOF mass spectrometry.

The elution step allows recovery not only of troponin I, but also of all the proteins bound thereto, i.e. troponin T and troponin C, which are subsequently detected by Western blot. Also degradation products of troponins are eluted and subsequently detected.

2.1. Dependent claims 12 and 13 are novel, as a correlation between the detected troponin and a clinical parameter (e.g. ACS) is not actually disclosed by D1. However, the claims are not inventive (article 33(3) PCT), as D1 explicitly suggests the use of mass spectrometry combined with affinity chromatography to identify troponin modifications correlated with diseases, in particular ACS.

3. Claims 13-64, with limitation discussed in point III.2, are also not inventive over D1, in view of its actual disclosure (see above, point 2.a) and its explicit suggestion (see above, point 2.1).

4. It si further noted that the claims are not concise (article 6 PCT), due to the high number of independent and dependent claims very similar in scope.